REMARKS

I. Amendments to the Specification and Claims

Applicants first amend the specification to update the priority application information, as discussed in the following section, and also to correct an inadvertent error in translating the application from French to English. Specifically, the French phrase "l'administration puisse précéder . . . l'application," at page 5, lines 23-25, of the original French version of PCT/FR98/01400 should be translated as "the administration can precede . . . the application" rather than "the administration can be preceded by . . . the application." Because this is simply an error of translation and because the original French PCT is incorporated herein by reference, this correction does not introduce new matter. Applicants respectfully request the entry of these amendments.

Claims 85-89, 91, 95-96, 98-102, and 104-120 are pending and under examination. Applicants thank Examiner Woitach for withdrawing the previous restriction and election requirements.

This Reply contains several claim amendments. First, claims 90, 92-94, 97, and 103 are canceled without prejudice or disclaimer.

Second, Applicants amend claim 85 to recite "a method of transferring nucleic acids into one or more striated muscles *in vivo*." This amendment is supported by the application as a whole, including original claims 1 and 2, for example. In parallel with this change, Applicants move the "at least one angiogenic factor" to new claim 118, and correct the dependency of claim 86 accordingly. Applicants also make claims 104, 107, 109, and 111-117 dependent on claim 85. The changes in dependency and the creation of claim 118 only re-phrase claims 85-117, and do not narrow their scope.

Third, Applicants correct the units of the "electric field intensity" to recite Volts per centimeter "V/cm" instead of "V/cm^2." This change is supported throughout the application as a whole, for example, at page 9, lines 9-17. One of ordinary skill in the art would also recognize that "V/cm" is the correct unit for the field intensity used in the art, and accordingly, that this amendment merely corrects an inadvertent typographical error, and does not alter the scope of the claims. (*See, e.g.,* R. Heller et al., *FEBS Lett.* 389: 225-228, Figure 1 (1996), for an example showing that "field intensity" is measured in "V/cm.")

Fourth, the range of the "electric field intensity" in claim 85 is changed from "1 to 800" to "4 to 400." A similar change is made to claim 98. Claim 97, which recited a range of 1 to 400, is canceled. Support for this amendment may be found throughout the application, including the text at page 9, lines 9-17, and original claims 2 and 44.

Finally, Applicants insert new claims 119 and 120. Claim 119 recites an "electric field intensity" of "30 to 300 V/cm." This claim is supported throughout the application, for example, at page 9, lines 9-17. Claim 120 is drawn to the method of claim 85 in which "contacting *in vivo* at least one striated muscle cell with at least one nucleic acid" precedes "electrically stimulating said at least one striated muscle cell." This claim is also supported throughout the application, for example at page 9, lines 4-8, and page 5, lines 23-25, of the original French-language PCT application.

In summary, all of the amendments and new claims are fully supported by the application as filed and do not introduce new matter. Applicants respectfully request their entry.

II. Objection to the Specification

The Office requests that Applicants amend the priority claim in the first paragraph of the application by including the current status of parent Application No. 09/341,350. (Office Action at page 3.) Applicants comply with that request and also list United States provisional Application No. 60/067,488 and French Application No. 97/08233 in that paragraph. (See the Declaration filed in Application No. 09/341,350, copy attached, and the Official Filing Receipt mailed July 17, 2002.)

III. Objection to the Oath/Declaration

The Office also objects to the Declaration filed in parent Application No. 09/341,350, asserting that, on page 2, it claims priority to PCT/FR98/01400 under 35 U.S.C. § 119, rather than states that Application No. 09/341,350 is the National Stage of PCT/FR98/01400. (Office Action at page 4.)

Applicants, however, are unable to locate the source of the Office's objection to the Declaration. For example, page 1 of the Declaration states in part: "I believe . . . I am an original, first and joint inventor . . . on the invention . . . the specification of which . . . was filed as PCT International Application Number PCT/FR98/01400 on June 30, 1998." (Emphasis added.) Thus, the Declaration correctly identifies the parent application as the National Stage of PCT/FR98/01400. Later on the same page, the Declaration claims priority under 35 U.S.C. § 119 to French Application No. 97/08233, and U.S. Provisional Application No. 60/067,488. Page 2 of the Declaration, which the Office cites, contains the power of attorney statements. (See the duplicate copy of the Declaration submitted herewith.)

Thus, Applicants request that this objection be withdrawn.

IV. Information Disclosure Statement

The Office also comments that the Information Disclosure Statement filed February 11, 2002, does not apparently include certain publications cited in the application. (Office Action at page 4.) Applicants attach an additional Information Disclosure Statement to this Reply that includes such documents.

V. Rejection under 35 U.S.C. § 112, Second Paragraph Is Moot

The Office rejects claims 90 and 92-94 as allegedly indefinite, asserting that a "striated muscle" as recited in claims 85 and 92, does not include "heart muscle" and that a "segment of striated muscle" is unclear. (Office Action at page 5.) This rejection is moot, as all of these claims are canceled.

VI. The Pending Claims Are Novel

The Office rejects claims 85, 103-106, and 111, under 35 U.S.C. § 102(a) or § 102(e), as allegedly anticipated by one or more of Dev et al. (WO 96/39226; "Dev I"), Dev et al. (U.S. Patent No. 5,993,434; "Dev II"), or Hoffman (U.S. Patent No. 6,241,701). (Office Action at pages 5-9.) Applicants traverse each of these rejections, and note that the rejections are moot as to claim 103, which is now canceled.

A *prima facie* case of anticipation requires that a single publication teaches, either expressly or inherently, each and every element or limitation of the claim, including any functional limitations. M.P.E.P. § 2131. Moreover, the disclosed elements or limitations must be "arranged as in the claim." *See, e.g., Richardson v. Suzuki Motor Co.,* 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). Thus, '[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a

person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v. Genentech, Inc.,* 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991).

The publications the Office cites here each fail this test. In addition, Hoffman is not prior art to this application. Therefore, all of Applicants' claims are novel, and Applicants respectfully request the Office to withdraw these rejections.

A. "Dev I" WO 96/39226 and "Dev II" U.S. Patent No. 5,993,434

The Office contends that Dev I anticipates claims 85, 103, and 104 under § 102(a), and that Dev II anticipates claims 85, 103-106, and 111 under § 102(e). Applicants disagree, because neither of these publications teaches each and every element of those claims, arranged in the manner claimed.

For example, claim 85 recites in part: "contacting *in vivo* at least one striated muscle cell with at least one nucleic acid, and electrically stimulating said at least one striated muscle cell with at least one unipolar pulse of an electric field intensity ranging from 4 to 400 V/cm." A publication cannot anticipate claim 85 unless it teaches each of these limitations.

Dev I does not describe "contacting *in vivo* at least one striated muscle cell with at least one nucleic acid" with one or more pulses from an "electric field intensity ranging from 4 to 400 V/cm." Instead, Dev I discloses electrotransfer into tumor cell lines at a field strength of 1,000 or 1,300 V/cm. (See Dev I at pages 17 and 18 and Figure 12b.) Applicants, on the other hand, have unexpectedly shown that transfer of nucleic acids into striated muscle cells *in vivo* can be substantially increased by subjecting the muscle to electrical pulses of much lower intensity, such as 4 to 400 V/cm. Thus, Dev I does not anticipate any of the pending claims.

Dev II appears to contain a similar disclosure to Dev I. Like Dev I, Dev II does not describe electrically stimulating at least one striated muscle cell with one or more unipolar pulses of an electric field intensity ranging from 4 to 400 V/cm. Instead, Dev II, like Dev I, discloses electrotransfer into tumor cell lines at a field strength of 1,000 or 1,300 V/cm. (See Dev II at columns 11 and 12 and Figure 12b.)

Thus, Dev II does not anticipate any of the pending claims. Accordingly, Applicants request the Office to withdraw these rejections.

B. "Hoffman" U.S. Patent No. 6,241,701

The Office also asserts that Hoffman anticipates claims 85, 103-106, and 111 under 35 U.S.C. § 102(e). However, Hoffman is not prior art to the instant application.

Hoffman was filed on October 22, 1998, and is a continuation in part of an application filed on August 1, 1997. (See Hoffman's cover page.) In contrast, the instant application is based on a PCT application filed on June 30, 1998, and claims priority to French Application No. 97/08233, filed on June 30, 1997.

Applicants attach a certified translation of the French application in order to demonstrate that Applicants were in possession of the instant invention prior to Hoffman's first filing date. Examples 1-5 and Figures 1-5 of the French application are essentially the same as those of the instant application. Examples 1 and 2, at pages 16-20 of the translation, and corresponding Figures 1A-B and 2A-B, demonstrate possession of claim 85. In those examples, nucleic acids were transferred into mouse muscle cells *in vivo*, using an electric field intensity of 200 or 400 V/cm. Examples 3-5 also show successful transfer using one or more unipolar pulses at a field intensity of 100 or 200 V/cm. Pages 9-13 of the translated French application list the applicable

genes encoded by the nucleic acids, including VEGF, Factors VII, VII, and IX, and others, and therefore, demonstrate possession of the subject matter of the instant claims 103-106 and 111.

Because Applicants were in possession of the subject matter of claims 85, 103-106, and 111 prior to Hoffman's first filing date, Hoffman is not prior art against this application, and Applicants request the withdrawal of this rejection.

VII. The Pending Claims Are Nonobvious

Finally, the Office contends that the pending claims are obvious over a combination of Dev I, Dev II, Hoffman, and two patents issued to Wolff et al., "Wolff I" (U.S. Patent No. 5,693,622) and "Wolff II" (U.S. Patent No. 6,228,844). (Office Action at pages 9-11.) Applicants respectfully disagree.

Hoffman is not prior art to any of the pending claims for the reasons presented above. For this reason alone, this combination of publications cannot render Applicants' claims obvious, and Applicants will not discuss Hoffman herein.

Applicants also traverse this rejection because the combination of the Dev and Wolff publications does not meet the requirements for a *prima facie* case of obviousness.[1]

A *prima facie* case of obviousness has three distinct requirements. First, the references must teach or suggest every claim element. M.P.E.P. §§ 2142 and 2143.03. Second, there must be a motivation to modify or combine the teachings of the cited

[1] Wolff I and Wolff II contain nearly identical disclosures, while Dev I and Dev II also contain similar disclosures. Thus, Applicants' remarks about Dev and Wolff apply equally to Dev I and II and to Wolff I and II.

references. M.P.E.P. §§ 2143 and 2143.01. Third, there must be a reasonable expectation of success in performing the modified or combined teachings of the references. M.P.E.P. § 2143.02.

The motivation to combine or modify references and the reasonable expectation of success must both come from the references themselves or from the knowledge generally available to one of ordinary skill in the art, and not by hindsight from the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2142. In addition, all of the teachings of the references must be considered in the obviousness inquiry. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). One cannot pick and choose only those elements of a reference that support a rejection while omitting other elements that do not support the rejection. *In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965).

The combination of Dev and Wolff fails this three-part test.[2] First, Dev and Wolff do not teach or suggest all of Applicants' claim limitations. As described above, Dev does not teach "electrically stimulating at least one striated muscle cell [*in vivo*] with at least one unipolar pulse of an electric field intensity ranging from 4 to 400 V/cm" as required by claim 85 and all of the other claims in this application. Instead, it teaches stimulating tumor cells with an electric field intensity of 1,000 or 1,300 V/cm. Thus, Dev does not teach or suggest the "electrically stimulating" limitation of Applicants' claimed method. Wolff does not remedy this deficiency in Dev because, as discussed below, it only mentions electroporation in passing, without comment as to any electric field intensity. Moreover, it only mentions electroporating cells *in vitro*, rather than *in vivo*, as

[2] Again, Hoffman is not considered here as it is not prior art to this application.

Applicants claim. Therefore, Dev and Wolff do not teach or suggest Applicants' "electrically stimulating" limitation.

There is also no motivation to combine Dev with Wolff. The Office contends that Wolff teaches electroporation at column 16, lines 56-64. Yet, the Office does not consider what Wolff actually teaches about electroporation. Far from recommending electroporation, Wolff teaches away from it.

Indeed, Wolff states that "[c]ationic lipid based transfection technology is preferred over other methods; it is more efficient and convenient than . . . electroporation methods." (Wolff I at col. 16, lines 58-61.) Further, this statement refers to transfection of cells *in vitro*, by taking cells out of the body, transfecting them in culture, then injecting them back into the body. (*Id.* at col. 16, lines 45-57.) Accordingly, Wolff goes on to recommend taking cells taken from the body and transfecting them *in vitro* using cationic liposomes. (*Id.* at col. 17, lines 6-13, and Examples 1, 6, and 22.) In contrast, Applicants claim methods of transfecting cells *in vivo*. Instead of recommending electroporation to transfect cells *in vivo*, Wolff recommends various direct injection techniques using catheters, needles, and vaccine guns. (Id. at col. 4, line 44, to col. 5, line 62, col. 9, line 49, to col. 10, line 12, and col. 16, lines 45-55.) In fact, Wolff does not even mention electroporation for transfection *in vivo*.

The Office also contends that Wolff "teach[es] that delivery can be accomplished by electroporation methodology *in vivo*" to muscle cells. However, Wolff does not teach that one should electroporate DNA into muscle cells *in vivo*. Instead, Wolff teaches that one should directly inject DNA into the interstitial space of muscle tissue, i.e. the space

between the cells, and allow the cells to take up the DNA unaided. (*Id.* at col. 9, line 49, to col. 10, line 12.) This also teaches away from Applicants' invention.[3]

Thus, careful consideration of what Wolff actually teaches as a whole demonstrates that Wolff teaches away from the instant invention. It teaches away from using electroporation *in vitro*, does not mention electroporation *in vivo*, and suggests that when delivering nucleic acids to muscle cells, one should use direct injection and should not use any method to induce the cells to take up the nucleic acids. Such teaching away is "strong evidence of unobviousness." *W.L. Gore & Assoc., Inc. v. Garlock, Inc.,* 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983).

Further, the Office has simply picked and chosen only so much of Wolff as might support a rejection without considering Wolff's teachings in their entirety. The M.P.E.P. counsels that this strategy does not support a *prima facie* case. M.P.E.P. § 2141.03, *and see, e.g., In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965). Such picking and choosing also demonstrates that the Office has impermissibly used hindsight to combine Dev with Wolff. As the Federal Circuit points out, the Office cannot use the application as a "guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims." *Grain Processing Corp. v. American Maize-Prods. Co.,* 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988).

Indeed, a motivation to combine references is based on what a person of ordinary skill in the art, reviewing those references, would *desire* to do, not just on what he would consider theoretically feasible. M.P.E.P. § 2143.01; *Winner v. Wang*, 53

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[3] See also Wolff et al., *Science* 247: 1465-1468 (1990) and *BioTechniques* 11: 474-485 (1991) for similar teachings.

U.S.P.Q.2d 1580, 1587-8 (Fed. Cir. 2000). Thus, there is no motivation to combine Dev and Wolff, and those publications do not provide any desire to use electroporation to introduce nucleic acids into striated muscle cells. Instead, one of ordinary skill in the art reading Dev and Wolff would infer that injecting nucleic acids into the interstitial spaces is the best way to transfect muscle cells.

Dev and Wolff also do not constitute a *prima facie* case of obviousness because their teachings, in light of the prior art, provide no reasonable expectation that one could successfully transfer nucleic acids into striated muscle cells *in vivo* using the low electric field intensities that the instant claims require. Again, Dev uses only electric field intensities of 1,000 or 1,300 V/cm, while Wolff mentions nothing about electric field intensities.

Lowering the electric field intensity is not simply a matter of changing a variable. Instead, those of ordinary skill in the art recognized prior to this invention that the intensity of the electric field directly affects the ability of cells to take up nucleic acids. Further, the art at the time of this invention taught that electric field strengths of more than 800 V/cm were necessary to efficiently introduce nucleic acids into cells *in vivo*. For example, Figure 1 of R. Heller et al. illustrates that luciferase DNA could not be introduced into rat liver at an electric field intensity of less than 1,000 V/cm. (*FEBS Lett.* 389: 225-228 (1996), previously made of record in this application.)

Heller's figure shows that the intensity of the electric field has a significant effect on the success of the transfection. Accordingly, one of ordinary skill in the art reviewing Dev's disclosure would not reasonably conclude that, just because 1,000 or 1,300 V/cm

is sufficient to introduce a nucleic acid efficiently into a tumor cell, much lower intensities would be sufficient to introduce nucleic acids into striated muscle cells.

Applicants' claim 100 also recites that the duration of the at least one unipolar pulse is "greater than 10 milliseconds." In contrast, Dev teaches pulses of 99 microseconds, or about 100 times shorter. (Dev I at page 17, line 13, and page 18, line 19.) As described immediately below, the duration of the pulse, like the electric field intensity, is not a simple variable. Instead, Applicants' working examples show that the pulse duration may have a significant effect on the uptake of nucleic acids into striated muscle cells as well as on the safety of the transfection procedure.

Applicants working examples illustrate that one of ordinary skill in the art following Dev's suggestions to use intensities of 1,000 or 1,300 V/cm would not successfully obtain the claimed invention. For instance, Example 1 uses the prior art electroporation conditions of 800 to 1,200 V/cm in order to introduce luciferase DNA into the striated muscle cells in the legs of mice. (Application at pages 30-33 and Figures 1A and 1B.) Surprisingly, pulses of 800 to 1,200 V/cm actually yielded lower signals of luciferase than the controls in which the DNA was simply injected. (Id. at page 32, and Figures 1A and 1B.) Moreover, these high field intensities also damaged the muscle tissue. (Application at page 33, lines 3-5.) In fact, these results as a whole support the teachings of Wolff to simply inject DNA into muscle tissue and allow the cells to take it up unaided.

Applicants' surprisingly discovered, however, that longer pulses of lower intensity, such as 100, 200, or 400 V/cm, are safe to the muscle tissue and can increase the luciferase intensity in the tissue over simple injection by 200-fold. (Application at

pages 33-36, and Figures 2-4.) This data is also summarized in a paper by the instant inventors, which is submitted herewith. (L.M. Mir et al., *Sciences de la Vie/Life Sciences* 321: 893-899 (1998).)

Thus, Applicants' data also show unexpected results. Such unexpected results alone can be sufficient for patentability, even when a claimed invention would otherwise have been found obvious. M.P.E.P. § 2144.09.

More recent data also supports the unexpected nature of Applicants' findings. For example, Figure 2 of J.M. Wells et al., submitted herewith, shows that an electric field strength of about 1,000 to 1,400 V/cm is necessary to introduce a gene into tumor cells. (*Gene Therapy* 7: 541-547 (2000), submitted herewith.) Figure 6 of Gilbert et al. shows that an intensity of about 1,500 to 2,000 V/cm is necessary to introduce luciferase into tumor cells. (*Techn. Cancer Res. Treat.* 1: 355-63 (2002), submitted herewith.) In both cases, lower intensities in the range that Applicants claim here did not work.

For all of these reasons, the combination of Dev I, Dev II, Hoffman, Wolff I, and Wolff II lacks all three requirements for a *prima facie* case of obviousness, while Applicants' invention also shows unexpected results. Thus, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not found herewith to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Dated: March 23, 2004

By: _____
Elizabeth A. Doherty
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Attachments: **Information Disclosure Statement, PTO Form 1449, with 53 Documents**
Copy of the Declaration of the Inventors
Certified Translation of French Application No. 97/08233